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New treatment strategies for elderly myeloma patients

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In the treatment of elderly patients, the new paradigm is the combination of the *old drug* melphalan with the *new drugs* thalidomide, lenalidomide or bortezomib.

In newly diagnosed multiple myeloma (MM) patients, the combination melphalan, prednisone and thalidomide (MPT) induces a fast tumor response with a high response rate, but evidence that this translate into improved outcome is limited. This multicenter trial compared the efficacy and the toxicity of oral MPT with oral melphalan and prednisone (MP) in previously untreated patients.[1,2] The MPT regimen included oral melphalan (4 mg/m^2 for 7 days) and prednisone (40 mg/m^2 7 days) for six four week cycles plus thalidomide (100 mg per day continuously until any sign of relapse or progressive disease) The MP regimen was as MPT without thalidomide. Patients treated with MPT experienced higher response rates and a longer time to progression (primary end points) than patients who did not receive thalidomide. The overall response rate was 76% for MPT and 48% for MP alone (p<0.0001), and the near complete response rates were 28% and 7%, respectively (p<0.0001). Median progression free survival in the MPT and in the MP groups was 33 months and 14 months, respectively (hazard ratio, 0.47; p<0.001). MPT increase median progression free survival by almost 19 months. The 2-yr survival rate was 82% in MPT patients and 65% in MP patients (hazard ratio, 0.68; p=0.2). In MPT group, 33 patients did not complete the 6 courses because of progression disease,[9] toxicity,[16] death,[2] and withdrawal of consent or lost to follow-up.[6] In MP group, 32 patients did not complete the 6 courses because of progression disease,[19] toxicity,[3] death,[3] and withdrawal of consent or lost to follow-up.[7] By looking at those patients who completed the assigned 6 cycles in both arms, the 2-yr survival rate was 90% in MPT patients and 71% in MP patients, the difference was statistically significant (hazard ratio, 0.39; p<0.01). Grade 3 or 4 adverse events were reported in 49% of patients treated with MPT and in 25% of those treated with MP: they included thromboembolism (12% versus 2% of patients), infections (10% versus 1%), peripheral neuropathy (10% versus 1%), and hematologic toxicity (22% versus 25%) respectively. In the first 64 patients who received MPT, grade 3-4 adverse events were reported in 58% of patients. In the last 65 MPT patients, the incidence of grade 3-4 adverse events was 40%. By comparing the first cohort with the second one, thromboembolism dropped from 22% to 3% (p<0.01) and neurotoxicity from 13% to 8% (p=NS), respectively. The oral MPT was superior to the standard MP in patients with newly diagnosed myeloma. The adequate mangement of side effects reduced toxicity. Similar results were obtained by the Facon et al. study3. In this trial, MPT was compared with MP but also with autologous transplant. MPT was significantly superior to MP and autologous transplant for both event-free survival and overall survival.

Lenalidomide (Revlimid®) is a novel, orally active immunomodulatory drug effective for the treatment of refractory myeloma. In this multicenter trial, we evaluate the potential additive and synergistic effect of the combination RevlimidR, melphalan and prednisone (R-MP). Patients (pts) with newly diagnosed symptomatic multiple myeloma older than 65 years were treated with 9 courses of RevlimidR (5-10 mg/day for 21days every 4-6 weeks) plus MP (melphalan 0.18-0.25 mg/kg and prednisone 2 mg/kg for 4 days every 4-6 weeks). The trial was designed to define the toxicity profile of R-MP and to analyze the efficacy of this combination4. Four different dose levels were tested: 1. melphalan 0.18 mg/kg + RevlimidR 5 mg/day; 2. melphalan 0.25 mg/kg + RevlimidR 5 mg/day; 3. melphalan 0.18 mg/kg + RevlimidR 10 mg/day; 4. melphalan 0.25 mg/kg + RevlimidR 10 mg/day. Each cohort included 6 pts. Dose limiting toxicity (DLT) was defined as: any grade > 3 non-hematologic toxicity; grade 4 neu-

tropenia lasting >7 days; any other grade 4 hematologic toxicity and any treatment delay due to toxicity that occurred during the first cycle. All pts received ciprofloxacin and aspirin as prophylaxis. At present, 24 pts (median age 72, range 61-77) received at least one R-MP course and were evaluated. No DLTs were observed in the first 2 dose levels; 1 DLT was observed with melphalan 0.18 mg/Kg and RevlimidR mg/kg (grade 4 neutropenia lasting> 7 days); 2 DLTs were reached with melphalan 0.25 and RevlimidR 10 mg (1 neutropenic fever, 1 grade 3 cutaneous toxicity). After 3 cycles of R-MP, myeloma protein reduction of 75-99% was detected in 1 patients (11,1%), response of 50-74% in 8 patients (55.6%) and response <50% in 5 patients (33.3%), no disease progressions were observed. Grade 3 or 4 adverse events were reported in 9 patients (35%). They included: 1 thromboembolism (4.2%); 5 grade 4 neutropenias (20.9%); 4 grade 3 neutropenias (16.7%); 4 grade 3 thrombocytopenias (16.7%); 1 febrile neutropenia (4.2%); 2 grade 3 dermatological toxicities (8.3%); 1 grade 3 metabolic toxicity (4.2%) and 1 grade 4 metabolic toxicity (4.2%). One pt discontinued RevlimidR because of grade 3 dermatological toxicity. Dose- reduction was required in 4 pts (1 grade 4 neutropenia >7 days, 1 treatment delay due to toxicity, 2 grade 3 dermatological toxicities). Conclusions. R-MP was well tolerated with a manageable toxicity. Significant response rate was observed. It represents a feasible and promising approach for newly diagnosed pts who are not candidates for transplant. Fifteen additional pts were treated with the fix dose of melphalan 0.18 mg/kg + RevlimidR 10 mg/day, results are too premature to assess efficacy.

Bortezomib is also undergoing investigation in the first-line setting for elderly patients. Mateos et al.5 conducted a Phase I/II study to evaluate the effect of adding bortezomib to melphalan and prednisone (MP) in elderly patients (aged ≥65 years) with untreated MM. The median age of the 60 enrolled patients was 74 years (range 65–85 years) with almost half of all patients (47%) aged >75 years. Analysis of response rates after cycle 1 revealed an ORR of 70% (6% CR, 2% nCR and 64% PR rates), demonstrating that response rates with a combination of bortezomib and MP (MPV) after only 1 cycle of therapy were significantly higher than those typically observed after 6 cycles of treatment with MP alone.4 Best-response analysis with MPV after a median of 5 cycles revealed an ORR of 86% (30% CR, 13% nCR, 43% PR rates); efficacy of MPV was comparable across all age groups (i.e. in patients aged <75 and >75 years). With a median follow-up of 10.5 months, event-free survival (EFS) and progression-free survival (PFS) were 85% and 93%, respectively.

Toxicity was manageable and similar to that previously observed in other bortezomib studies. The most common grade 3/4 toxicities included thrombocytopenia (52%), neutropenia (43%), infection (17%), diarrhea (17%), and anemia (10%). Thirty-five per cent of patients required bortezomib dose reduction, mostly due to neuropathy. Peripheral neuropathy was found to be more common in patients aged >75 years than in those aged <75 years, possibly due to the generally more frail physical condition of the older patients. Overall, toxicities were found to decrease after cycle 3.

Based on the positive results of the Phase I/II MPV study, a Phase III, multicenter, international trial of bortezomib in combination with MP versus MP alone is currently ongoing in patients with newly diagnosed disease who are not transplant candidates. The study will assess the efficacy, overall safety, and tolerability of MPV versus MP alone, and will examine whether MPV is superior to MP, the current standard of care in elderly patients with MM.

References

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